



INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Department of Obstetrics and Gynecology

MATERNAL AND FETAL METHADONE EXPOSURE: Associations with neonatal abstinence syndrome (NAS)

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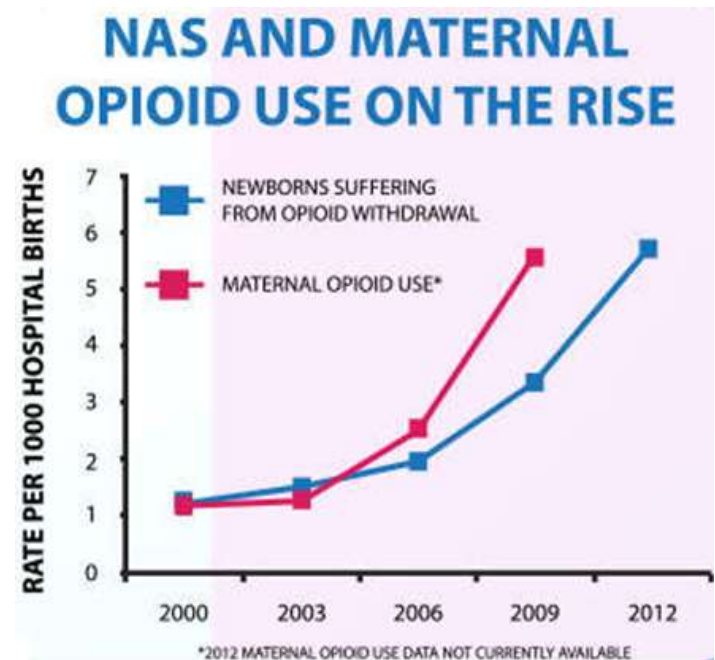
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The opiate epidemic and increasing NAS

Methadone and **buprenorphine** are recommended as long-term treatment for opioid use disorder in pregnancy.

METHADONE:

- Opioid analgesic (morphine analog) with long half-life (~22 hours - adults)
- Racemic mixture of **R-Methadone** and **S-Methadone** (**R** is more potent than **S**)
- Metabolized by CYP450 enzymes to R- and S-EDDP (CYP3A4, CYP2B6, aromatase, and CYP2C19).



Patrick et al., *Journal of Perinatology*, 2015; Kharasch ED. *Clin Pharmacol Drug Dev.* 2017

<https://www.drugabuse.gov/related-topics/trends-statistics/infographics/dramatic-increases-in-maternal-opioid-use-neonatal-abstinence-syndrome>

Neonatal Abstinence Syndrome (NAS)

Drug withdrawal syndrome that occurs primarily among opioid-exposed infants shortly after birth.

Up to 97% of newborns exposed to **methadone** in utero will require pharmacologic treatment (unable to predict NAS severity).

WITHDRAWAL SYMPTOMS (most commonly occur 48–72 hours after birth):

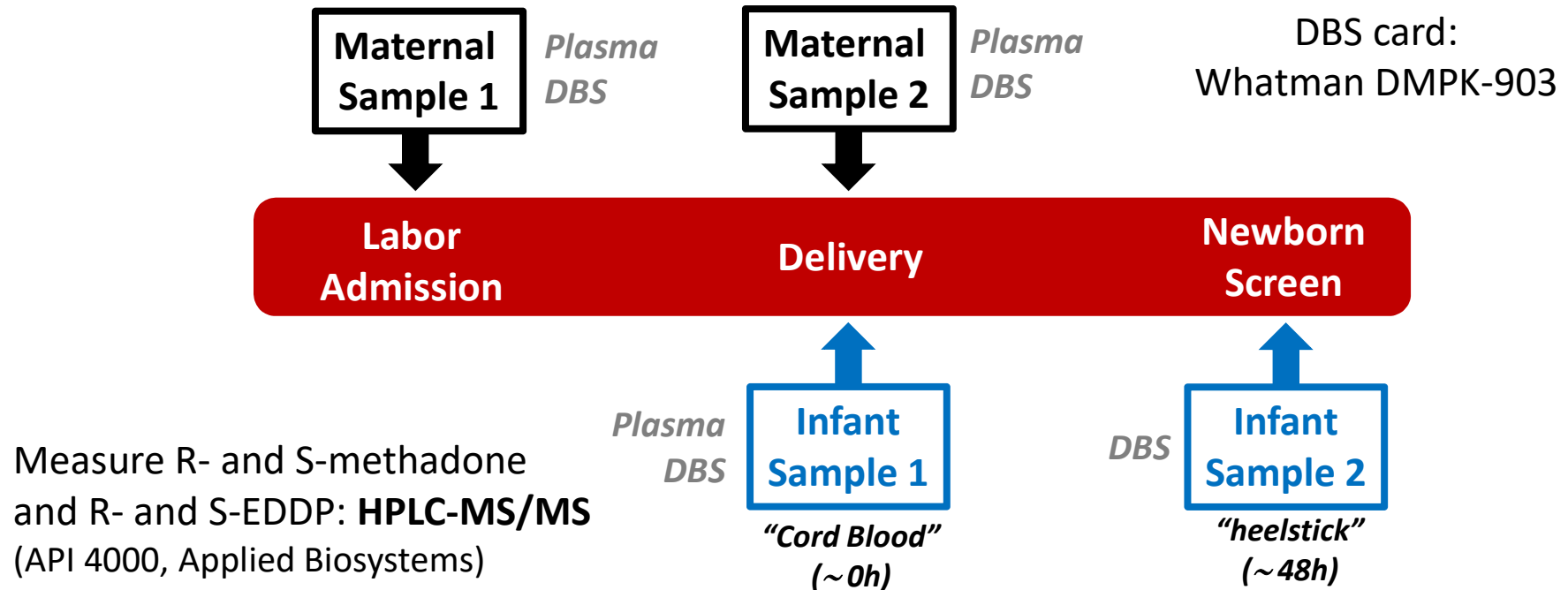
- Extreme irritability
- Increased muscle tone
- Difficulty sleeping
- Poor feeding
- Diarrhea
- Temperature instability
- Seizures (severe cases)



OBJECTIVE

Determine whether increased neonatal methadone exposure increases the severity of neonatal abstinence syndrome (NAS)

METHODS



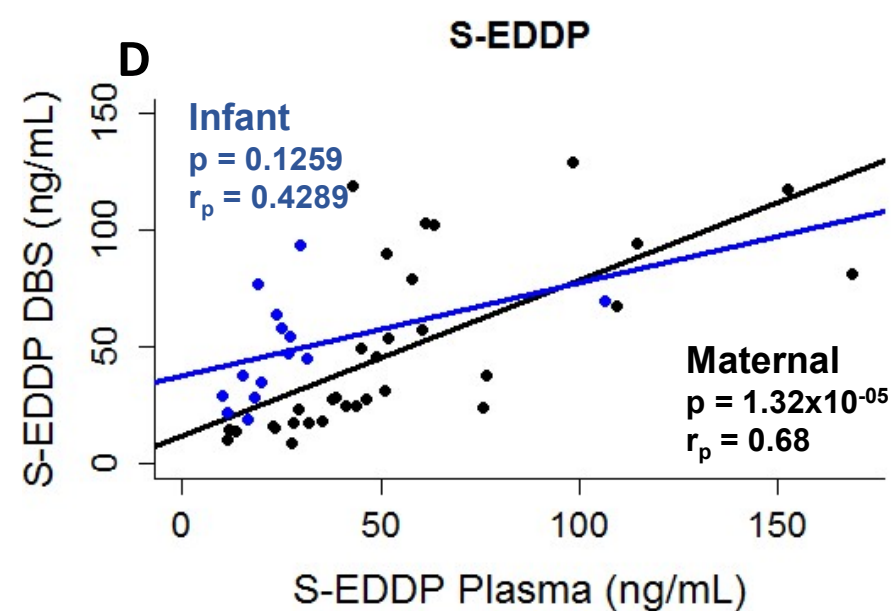
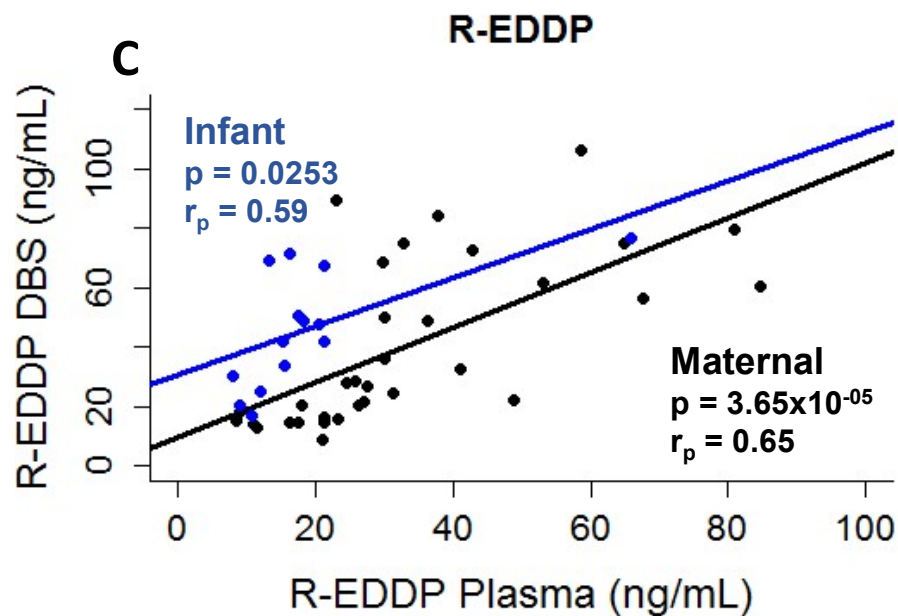
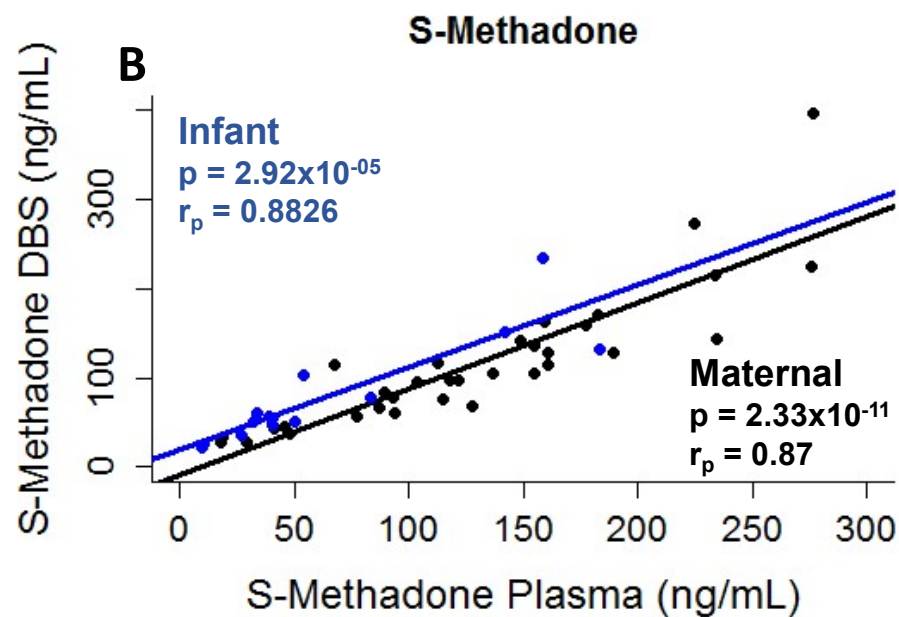
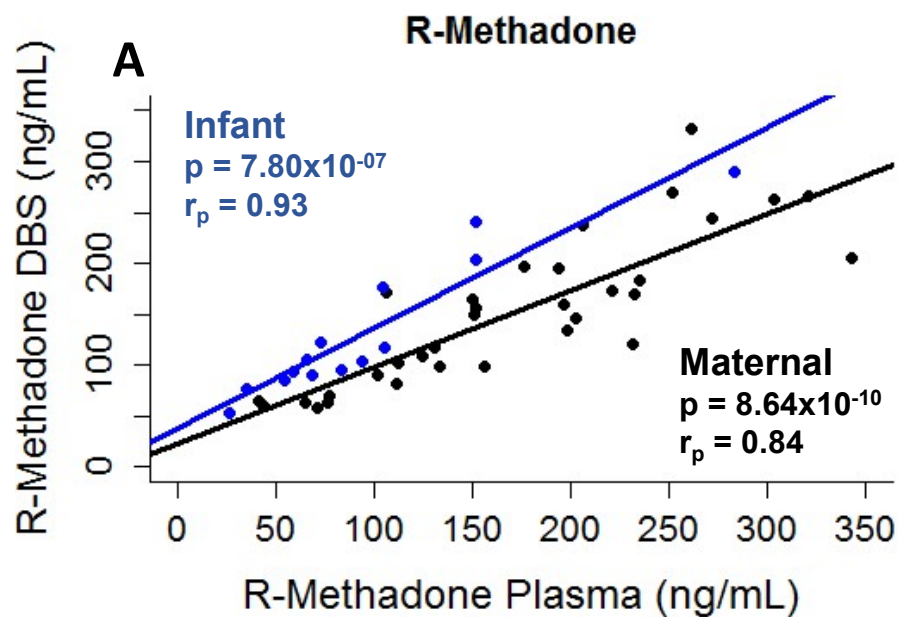
NAS protocol

- At our institution, Finnegan score is used to monitor NAS severity (e.g.: continuous high pitched cry, hours slept, tremors, convulsions, fever, respiratory rate, poor feeding, gastrointestinal disturbance)
- After 3 consecutive scores >8 or a single score >=12, treatment is initiated with morphine (Phenobarb may also be added for refractory NAS)

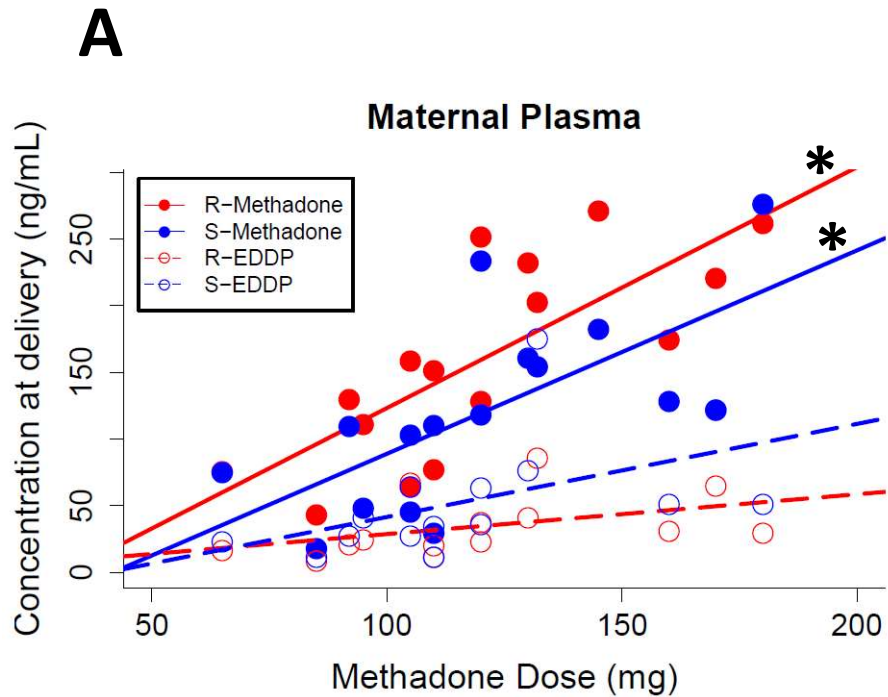
SUBJECT DEMOGRAPHICS AND RESULTS

	NAS (N = 16)	no NAS (N = 4)	P value
Dose	110 (60 - 170)	131 (95 - 180)	0.2011
Maternal age (years)	28 (23 - 42)	35 (24 - 35)	0.2547
Ethnicity (NH/L / H/L)	15 / 1 (94% / 6%)	4 / 0 (100% / 0%)	1.0000
Race (White/Black/Unknown)	15 / 0 / 1 (95% / 0% / 6%)	2 / 2 / 0 (50% / 50% / 0%)	0.1883
Height (cm)	164 (152 - 175)	160 (152 - 173)	0.4757
Weight (kg)	86 (56 - 114)	79 (58 - 90)	0.5080
BMI	31 (22 - 43)	29 (23 - 35)	0.6033
Gestational age at delivery (weeks)	38 (35 - 41)	39 (37 - 40)	0.8128
Birth Weight (kg)	3 (2.3 - 3.7)	2.6 (2.4 - 2.9)	0.2019
Sex of Infant (Female / Male)	8 / 8 (50% / 50%)	2 / 2 (50% / 50%)	1.0000
Breastfeeding (Yes / No)	6 / 10 (38% / 63%)	3 / 1 (75% / 25%)	0.2848
1 minute APGAR score	9 (1 - 9)	9 (7 - 9)	0.3202
Peak Finnegan Score	13 (10 - 20)	9 (7 - 10)	0.0034 *
Number of days in hospital	29 (19 - 55)	6 (5 - 6)	0.0029 *
Peak morphine dose (mg/day/kg)	0.05 (0.02 - 0.61)		
Total cumulative morphine dose (mg/kg)	5.64 (1.02 - 17.53)		

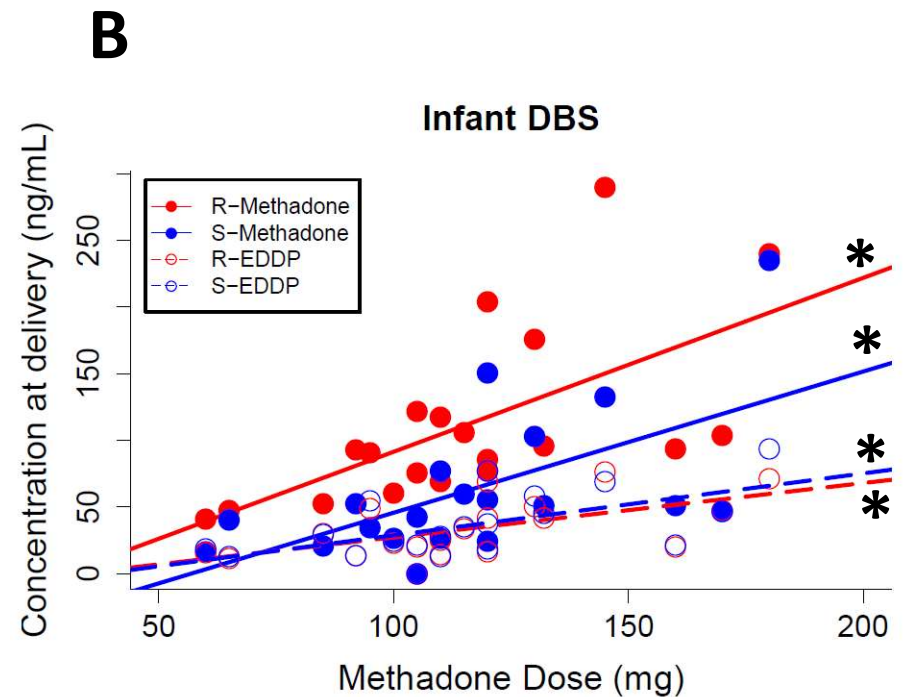
Correlations between plasma and DBS concentrations



Delivery concentrations are correlated with maternal methadone dose

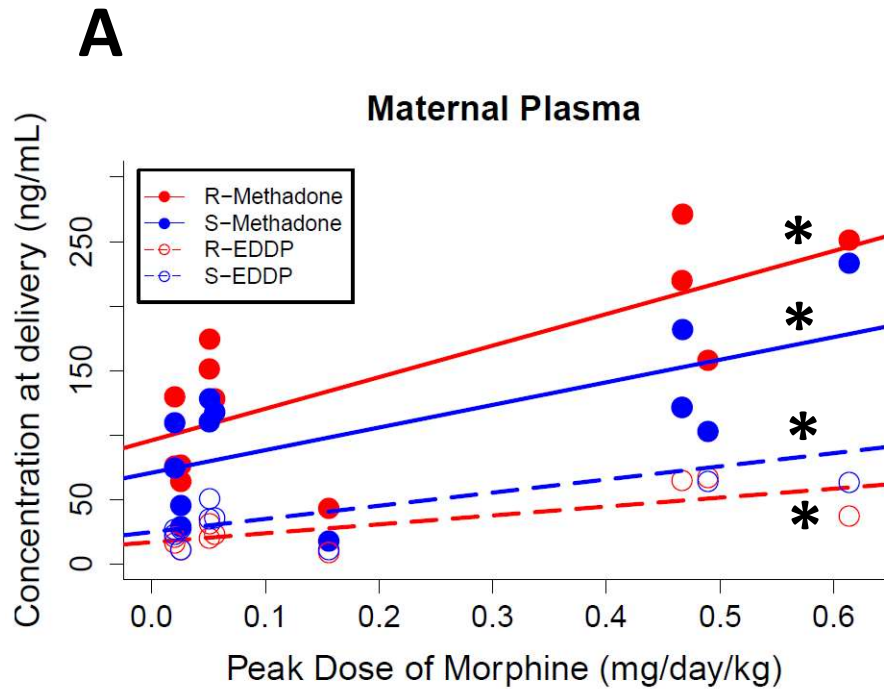


$r_p \sim 0.7$

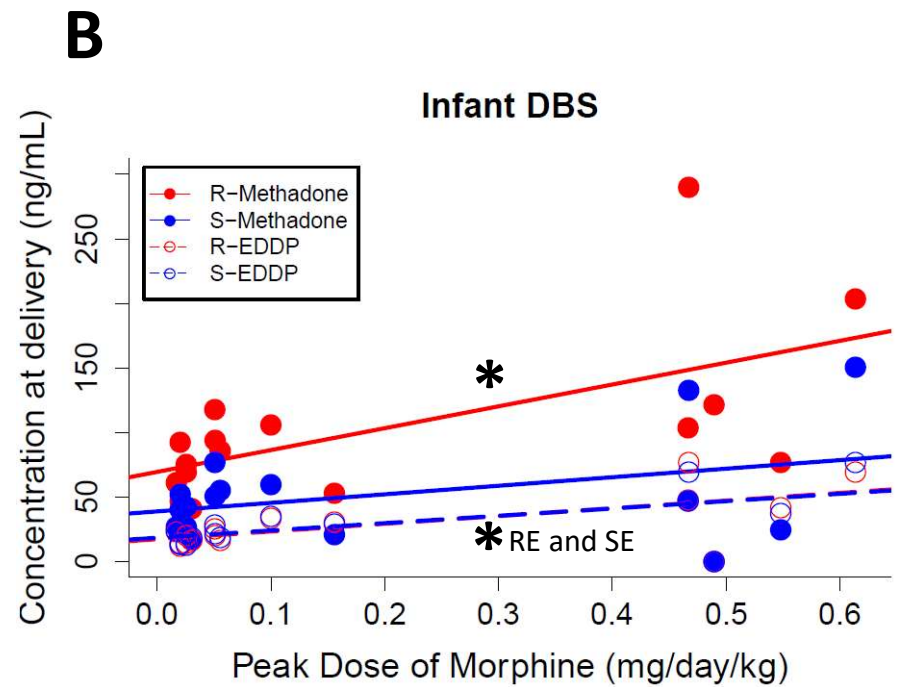


$r_p \sim 0.6$

Delivery concentrations are correlated with peak morphine per kg



$r_p \sim 0.7$



$r_p \sim 0.6$

CONCLUSIONS

- DBS collection on Whatman 903 paper may be a potential substitute for plasma methadone quantification but not for its metabolites.
- This pilot data indicates that maternal methadone AUC and cord blood concentration at delivery may be potential markers for NAS severity as measured by Finnegan score.
- Additional studies, with more objective markers of NAS, are needed to further understand the association between maternal and infant exposure to methadone and NAS.

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